REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following reasons.

I. Status of the Claims

Claims 25-35 and 76-86 were cancelled previously. No claim amendment is made in this response. Claims 1-24, 36-75 and 87-99 are pending and under examination.

II. Summary of the Claimed Invention

Applicants' claimed invention is directed to compositions comprising particles of glipizide or a salt thereof having an effective average particle size of less than about 2000 nm, and at least one surface stabilizer. Also claimed are methods of making and using such glipizide compositions.

Benefits of the claimed composition over prior art glipizide antagonist compositions include: (1) faster onset of action; (2) a potential decrease in the frequency of dosing; (3) smaller doses of glipizide required to obtain the same pharmacological effect; (4) increased bioavailability; (5) an increased rate of dissolution; (6) improved performance characteristics for oral, intravenous, subcutaneous, or intramuscular injection, such as higher dose loading and smaller tablet or liquid dose volumes; (7) improved pharmacokinetic profiles, such as improved T_{max}, C_{max}, and AUC profiles; (8) substantially similar or bioequivalent pharmacokinetic profiles of the nanoparticulate glipizide compositions when administered in the fed versus the fasted state; (9) bioadhesive glipizide formulations, which can coat the gut or the desired site of application and be retained for a period of time, thereby increasing the efficacy of the drug as well as eliminating or decreasing the frequency of dosing; (10) high redispersibility of the nanoparticulate glipizide particles present in the compositions of the invention following administration; (11) the nanoparticulate glipizide compositions can be formulated in a dried form

which readily redisperses; (12) low viscosity liquid nanoparticulate glipizide dosage forms can be made; (13) for liquid nanoparticulate glipizide compositions having a low viscosity - better subject compliance due to the perception of a lighter formulation which is easier to consume and digest; (14) for liquid nanoparticulate glipizide compositions having a low viscosity - ease of dispensing because one can use a cup or a syringe; (15) the nanoparticulate glipizide compositions can be used in conjunction with other active agents; (16) the nanoparticulate glipizide compositions can be sterile filtered; (17) the nanoparticulate glipizide compositions are suitable for parenteral administration; and (18) the nanoparticulate glipizide compositions do not require organic solvents or pH extremes. See specification, paragraph [0030] bridging pages 7 and 8.

III. Rejection of Claims under 35 U.S.C. §103(a)

The Examiner maintains the following rejections:

(1) Claims 1-15, 17-24, 40-75 and 87-90 remain rejected under 35 U.S.C. §103(a) for allegedly being obvious over U.S. Patent No. 5,510,118 to Bosch et al. ("Bosch") in view of PCT Publication No. WO 98/31360 by Stamm et al. ("Stamm");

(2) Claim 16 remains rejected under 35 U.S.C. §103(a) for allegedly being obvious over Bosch in view of Stamm, and further in view of GB 2316316 to Baralle et al. ("Baralle"); and

(3) Claims 36-39 remain rejected under 35 U.S.C. §103(a) for allegedly being obvious over Bosch in view of Stamm, and further in view of U.S. Patent No. 4,389,397 to Lo et al. ("Lo").

The Examiner further imposes a new rejection of claims 91-99 under 35 U.S.C. §103(a) for allegedly being obvious over Bosch in view of Stamm and U.S. Patent No. 5,939,091 to Eoga et al. ("Eoga").

Applicants respectfully traverse each rejection.

A. The Examiner's rejection based upon Bosch and Stamm hinges upon the erroneous assumption that all poorly water soluble active agents can be successfully and routinely made into nanoparticulate active agent compositions, and that such compositions have improved properties.

Because all of the rejections rely on the same primary reference, Bosch, and the same secondary reference, Stamm, Applicants choose to address the rejections collectively in the following paragraphs.

The Examiner asserts that it would have been obvious to select the glipizide active agent of Stamm and formulate the glipizide active agent into a nanoparticulate active agent composition using Bosch's process because: (i) glipizide is a well known water-insoluble drug; (ii) there is an art-recognized need to improve dissolution and bioavailability of glipizide; and (iii) Bosch's formulation is suitable for improving bioavailability of a wide variety of active agents including anti-diabetic agents.

In the prior response filed on August 10, 2011, Applicants submitted that, on the strength of a declaration under 37 C.F.R. §1.132 executed by Dr. Gary Liversidge ("the Liversidge Declaration"), the Examiner's presumptions that: (i) all poorly water soluble active agents can be successfully formulated into nanoparticulate active agent compositions; and (ii) all nanoparticulate active agent compositions would necessarily improve the bioavailability of the active agents, are ***incorrect***. To the contrary, the Liversidge Declaration establishes that: (i) not all active agents can be successfully formulated into nanoparticulate active agent compositions; and (ii) even if a nanoparticulate active agent composition can be made, the nanoparticulate active agent formulation does not necessarily improve the bioavailability of the active agent in comparison to a microparticulate formulation of the same active agent. Accordingly, in the absence of any predictability in the art, the Examiner has failed to established a *prima facie* case of obviousness.

In this final Office Action, the Examiner dismissed the declaration evidence for "failing to outweigh the evidence of obviousness" on the following grounds:

(1) the declaration evidence refers "only to the system described in the above referenced application and not to the individual claims of the application. Therefore, the Examiner deems the evidence not commensurate in scope with the claims;

(2) U.S. Patent No. 7,217,431 is not cited in the rejections;

(3) Ketoprofen cited in the declaration is not the active agent of the claimed invention; and

(4) the teachings of U.S. Patent No. 7,217,431 do not include the use of surfactant to improve bioavailability.

See final Office Action, the paragraph bridging pages 6 and 7. Applicants respectfully submit that the Examiner's dismissal of the declaration evidence is erroneous because the Examiner misunderstood the declaration.

B. The Liversidge Declaration establishes the unpredictability of the art in terms of making successful stable nanoparticulate active agent formulations, as well as the inability to predict the properties of such nanoparticulate active agent formulations.

As submitted in the prior response, the Liversidge Declaration establishes the unpredictability of the art in terms of the prospects of obtaining nanoparticulate active agent compositions and improving bioavailability by way of nanoparticulate active agent formulations. In other words, the Liversidge Declaration does not intend to submit unexpected results achieved by the claimed invention to overcome a *prima facie* case of obviousness. Rather, the Liversidge Declaration establishes unpredictability in the art to support Applicants' arguments that the Examiner has not met the initial burden to demonstrate a *prima facie* case of obviousness.

Therefore, the Examiner's argument that the evidence is not commensurate in scope with the claimed invention is irrelevant. MPEP 716.02(d) only requires that unexpected results to be

commensurate in scope with the claims, which does not apply to the Liversidge Declaration on the record.

For the same reason, it is irrelevant that U.S. Patent No. 7,217,431 is not cited by the Examiner in the rejection and that ketoprofen cited in the declaration is not the active agent of the claimed invention. This is because both the '431 patent and ketoprofen are submitted as evidence to show that nanoparticulate formulations of these active agents *did not improve the bioavailability of these active agents in comparison to the non-nanoparticulate formulations of these active agents*. This data is relevant and significant as the Examiner asserts, as part of the obviousness rejection based upon Bosch and Stamm, that one of skill in the art would take the glipizide compound of Stamm and formulate it into a nanoparticulate active agent composition using the method of Bosch to improve the bioavailability of glipizide as "all nanoparticulate active agent compositions would necessarily improve the bioavailability of the active agents."

Because the Examiner's presumption that all nanoparticulate active agent compositions improve the bioavailability of the active agents lacks any factual basis, as demonstrated by the Liversidge Declaration, the Examiner's basis for the obviousness rejection is lacking; if one of skill in the art cannot predict that a successful nanoparticulate active agent composition can be made, nor whether such a composition will have improved properties (which is what the Liversidge Declaration teaches), then there is no motivation to combine the teachings of Bosch and Stamm with any predictability of success in obtaining the claimed invention..

C. The Examiner's statement that the teachings of U.S. Patent No. 7,217,431 do not include a surface stabilizer is false.

Finally, the Examiner's assertion that the teachings in U.S. Patent No. 7,217,431 do not include the use of surfactants in combination with a nanoparticulate active agent to improve bioavailability lacks factual support. At the outset, the surfactants are not intended to improve bioavailability. Rather, the surfactants are used to adsorb on the surface of the nanoparticulate

active agent particles to prevent the nanoparticulat active agent particles from aggregation or agglomeration.

Moreover, paragraph 5 and Table 1 of the Liversidge Declaration explicitly discuss that Formulation A, which is a nanoparticulate active agent suspension, comprises a surfactant, hydroxypropyl cellulose (HPC-SL), as the surface stabilizer. The bioavailability of this nanoparticulate formulation (Formulation A) is compared with other non-nanoparticulate formulations (Formulations B-E). As demonstrated in paragraphs 6 and 7 and Table 2, the nanoparticulate formulation comprising HPC-SL as the surface stabilizer exhibited the lowest level of bioavailability, in comparison to other microparticulate formulations of the same active agent, as represented by the C_{max} and AUC values.

D. Baralle and Lo fail to address the deficiencies of Bosch and Stamm.

The tertiary references, Baralle and Lo, are cited for the alleged teachings of a bimodal particle distribution (Office Action, the paragraph bridging pages 4 and 5) and of the viscosity of the liquid dosage form (*id.*, at page 5, last two paragraphs), respectively. Additionally, new reference Eoga is cited for the alleged teaching of a fast melt tablet comprising nanoparticles of a poorly water soluble active agent. *Id.*, page 6, 2nd and 3rd paragraphs. None of the tertiary references compensate for the deficiencies of the primary and secondary references as detailed above.

In view of the foregoing, the Examiner has no valid basis to dismiss the declaration evidence. Applicants respectfully request that the Examiner give full consideration to the declaration evidence and withdraw the rejections under 35 U.S.C. §103(a).

CONCLUSION

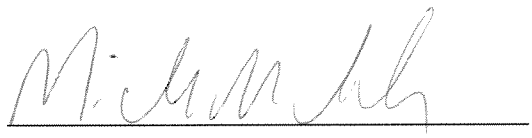
The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the

undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16 - 1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date: March 13, 2012

By 

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